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# Rectal cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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## incidence

The crude incidence of rectal cancer in the European Union is approximately 35% of the total colorectal cancer incidence, i.e. 15–25/100 000 per year. The mortality is 4–10/100 000 per year with the lower figures valid for females, the higher for males.

## diagnosis

Diagnosis is based on a clinical rectal examination including rigid proctoscopy with biopsy for histopathological examination. Tumors with distal extension to 15 cm or less (as measured by rigid proctoscopy) from the anal margin are classified as rectal, more proximal tumors as colonic.

## staging and risk assessment

Complete history and physical examination, complete blood count, liver and renal function tests, carcinoembryonic antigen (CEA), chest X-ray (alt. CT-scan) and CT or MRI or ultrasound of liver and abdomen should be performed.

Endoscopic ultrasound for the earliest tumors (cT1-T2) or rectal MRI for all others is recommended in order to select patients for preoperative treatment. Complete colonoscopy pre-or postoperatively is required.

Histopathological examination should include surgical specimen with proximal, distal and circumferential margins and regional lymph nodes (at least 12 nodes are recommended to be examined) and report on the degree of tumor differentiation and presence or absence of extramural venous invasion.

The TNM 2002 staging system (Table 1) should be used.

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## treatment

### localized disease

*overall strategy.* An important aim is to treat so that the risk of residual disease in the pelvis, frequently causing a disabling local recurrence, is very low (preferably less than about 5% in the population in whom curative treatment is intended) and, at the same time, with as little acute and late morbidity as possible. This should be possible in all but the few (≤10%) cases presenting with a fixed tumour growing into a non-readily resectable organ.

Another aim is to treat so that a good sphincter function can be preserved in as many patients as possible.

*need for quality assurance and control.* Treatment of rectal cancer is demanding and requires great skill in the entire multidisciplinary team. Good pathology and long-term complete follow-up, also including functional aspects, are important for quality control.

*risk-adapted treatment.* In the earliest, most favorable cases (T1-2, some early T3, N0 [T3a(-b) according to MR]) above the levators, surgery alone, either a local procedure, e.g. using the transanal endoscopic microdissection (TEM) technique in appropriately selected cases (T1, N0 [III, A]) or a sharp radical dissection using the total mesorectal excision (TME) technique [II, A].

In more locally advanced cases (most T3 (T3b+ according to MRI), some T4 (e.g. vaginal or peritoneal involvement only), N+), preoperative radiotherapy is recommended followed by TME, since this reduces local recurrence rates [I, A]. 25 Gy, 5 Gy/fraction during the week followed by immediate surgery is a convenient, simple and low-toxic treatment [I, A]. More demanding, but not more effective alternatives [II, A] are 46–50 Gy, 1.8–2 Gy/fraction without or with 5FU (bolus, continuous infusion or peroral) [III, A]. Whenever possible, preoperative treatment is preferred since it is more effective and less toxic than postoperative treatment [1, A].

In the most locally advanced, frequently non-resectable cases (T3 crm+, T4 with overgrowth to organs not readily resectable [T4a]), preoperative radiochemotherapy, 50 Gy, 1.8 Gy/fraction with concomitant 5FU-based therapy should be used [II, A], followed by radical surgery 6–8 weeks later. In very old patients (≥80–85+ years) and in patients not fit for

**Table 1.**

| TNM | Stage | Extension to |
|---|---|---|
| Tis N0 M0 | 0 | Carcinoma *in situ* |
| T1 N0 M0 | I | Submucosa |
| T2 N0 M0 | I | Muscularis propria |
| T3 N0 M0 | IIA | Subserosa/perirectal tissue |
| T3a | | Less than 1 mm |
| T3b | | 1–5 mm |
| T3c | | 5–15 mm |
| T3d | | 15+ mm |
| T4 N0 M0 | IIB | Perforation into perirectal tissue or invasion to other organs |
| T1-2 N1 M0 | IIIA | 1–3 regional nodes involved |
| T3-4 N1 M0 | IIIB | 1–3 regional nodes involved |
| T1-4 N2 M0 | IIIC | 4 or more regional nodes involved |
| T1-4 N1-2 M1 | IV | Distant metastases |

radiochemotherapy, 5 × 5 Gy with a delay before surgery can be a valid option [IV, A].

*postoperative therapy.* Postoperative chemoradiotherapy (e.g. 50 Gy, 1.8–2.0 Gy/fraction) with concomitant 5FU-based chemotherapy is no longer recommended but could be used in patients with positive circumferential margins, perforation in the tumor area or in other cases with high risk of local recurrence if preoperative radiotherapy has not been given [I, A].

Similar to the situation in colon cancer stages III (and 'high-risk' stage II), adjuvant chemotherapy can be provided, even if the scientific support for sufficient effect is less [II, A]. It appears as if the efficacy of adjuvant chemotherapy is less if the tumors have not responded to the (chemo)radiotherapy [IV, A].

### local recurrences

Patients with recurrence (if radiotherapy was not given in the primary situation) may receive preoperative radiotherapy with concomitant chemotherapy [II, A].

In patients previously irradiated, attempts at providing additional radiotherapy, externally or using brachytherapy or intraoperative radiotherapy (IORT) could be tried depending on normal tissue tolerance doses [IV, D].

Attempts of radical surgery should take place 6–8 weeks after radiotherapy [II, A].

In patients with prior radiotherapy for whom salvage surgery is not an option, systemic chemotherapy should be considered [I, A].

### disseminated disease

Whether patients with primarily disseminated disease (synchronous metastases) first should receive the locoregional treatment and then the systemic treatment, or the reverse, is poorly known [IV, D]. Age, co-morbidity, patient preferences, extent of primary and metastatic disease must be considered.

In selected cases treatment may include surgery of resectable liver or lung metastases [III, A]. Other surgical or stenting procedures [III, A] or radiotherapy should be considered as palliative procedures [II, A].

First line palliative chemotherapy should be considered early and consists of 5-FU/leucovorin in various combinations and schedules with oxaliplatin or irinotecan, with or without bevacizumab [I, A] or cetuximab in patients with non-mutated K-ras tumors [I, A].

Second line chemotherapy should be considered for patients with maintained good performance status [I, A] and third line therapy for selected patients, also in good performance status [II, A].

## follow-up

Follow-up serves to identify patients in need of salvage surgery or palliative care and to prevent second colorectal cancers. There is no strong proof that regular follow-up after successful treatment improves the outcome of patients with rectal cancer. A provisional recommendation is:

- History and rectosigmoidoscopy (if possible) every 6 months for 2 years [V, D]. A completion colonoscopy if not done at the time of diagnostic work-up (e.g. obstruction) should be performed within the first year.
- History and colonoscopy with resection of colonic polyps every 5 years [I, B].
- Clinical, laboratory and radiological examinations are of unproven benefit and should be restricted to patients with suspicious symptoms [A].

## note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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